

Combination Nucleos(t)ide Analogue as Initial Treatment for Chronic Hepatitis B: Have We Put This to Rest?

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Combination nucleos(t)ide analogs (NUCs) had been advocated as the initial treatment of chronic hepatitis B when lamivudine and adefovir dipivoxil (ADV) were the only approved NUCs for hepatitis B. These drugs had weak antiviral activity and/or low barrier to resistance with rates of genotypic resistance of 70% and 29%, respectively, after 5 years of continuous treatment.^{1,2} Borrowing from lessons learned in development of treatment for human immunodeficiency virus infection, virologists warned that a combination of NUCs with no cross-resistance would be necessary to maintain long-term suppression of hepatitis B virus (HBV) replication.

In the past 7 years, three additional NUCs have been approved for hepatitis B. Of these, entecavir (ETV) and tenofovir disoproxil fumarate (TDF) have been shown to have a very high barrier to resistance. Phase III clinical trials found that the incidence of genotypic resistance was 1.2% and 0% after 5 years of ETV and TDF monotherapy in NUC-naïve patients, respectively.^{3,4} Among hepatitis B e antigen (HBeAg)-positive patients, 94% of ETV-treated patients had HBV DNA <300 copies/mL and 97% of TDF-treated patients had HBV DNA <400 copies/mL at Year 5.^{4,5} Although the design of both trials left room for doubt, these data showed that monotherapy with ETV or TDF can maintain viral suppression in the vast majority of patients with chronic hepatitis B for at least 5 years.

In the phase III ETV trial, only 183 of 354 patients were enrolled in the roll-over study, some patients had a short gap in treatment between Years 2 and 3, a small number of patients received a combination of lamivudine and ETV for a short duration, and all patients received a higher dose of ETV (1.0 mg) from Year 3 onward.⁵ Nevertheless, other studies in which ETV 0.5 mg was administered continuously confirmed that >90% of patients had undetectable HBV DNA and 0%-1% had genotypic resistance after 3-4 years of treatment (Fig. 1).⁶⁻¹⁰ In the phase III TDF trial, patients with confirmed HBV DNA ≥ 400 copies/mL on or after Week 72 were eligible to add emtricitabine (FTC) to TDF and 34 of 51 eligible patients did so.^{4,11} A multicenter field study of TDF monotherapy in Italy confirmed that HBV DNA was undetectable in 95% HBeAg-positive and in 98% HBeAg-negative patients at Year 3 in the absence of FTC rescue.¹²

These additional studies support the optimism that monotherapy with ETV or TDF would be sufficient for the vast majority of NUC-naïve patients with chronic hepatitis B. A lingering question is whether this optimism can be applied to patients with high baseline viral load.

In this issue of *Hepatology*, Gordon et al.¹³ reported the results of a subgroup analysis of the phase III TDF trial. Eligible patients (HBeAg-positive and HBeAg-negative) were randomized to receive TDF 300 mg daily or ADV 10 mg daily for 48 weeks and then open-label TDF for an additional 192 weeks. Of 641 patients enrolled in the trial, 129 (118 HBeAg-positive) had high baseline viral load (HVL) defined as HBV DNA ≥ 9 log₁₀ copies/mL (8.24 log₁₀ IU/mL). At Week 240 (~Year 5), 96.1% of HVL and 98.7% of non-HVL patients on treatment achieved HBV DNA <400 copies/mL. Both groups had similar rates of histologic regression between baseline and Week 240. Patients with HVL generally took longer to achieve HBV DNA <400 copies/mL but had caught up with the non-HVL patients by Week 96. The authors stated that no patient with baseline HVL had persistent viremia at Week 240 or amino acid substitutions associated with TDF resistance.

These results are remarkable and suggest that monotherapy with a potent NUC that has a high barrier to

Abbreviations: ADV, adefovir dipivoxil; ETV, entecavir; FTC, emtricitabine; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HVL, high baseline viral load; NUCs, nucleos(t)ide analogs; TDF, tenofovir disoproxil fumarate.

Address reprint requests to: Anna S.F. Lok, M.D., Division of Gastroenterology and Hepatology, University of Michigan Health System, 1500 East Medical Center Dr., 3912 Taubman Center, SPC 5362, Ann Arbor, MI 48109. E-mail: aslok@umich.edu; fax: 734-936-7392.

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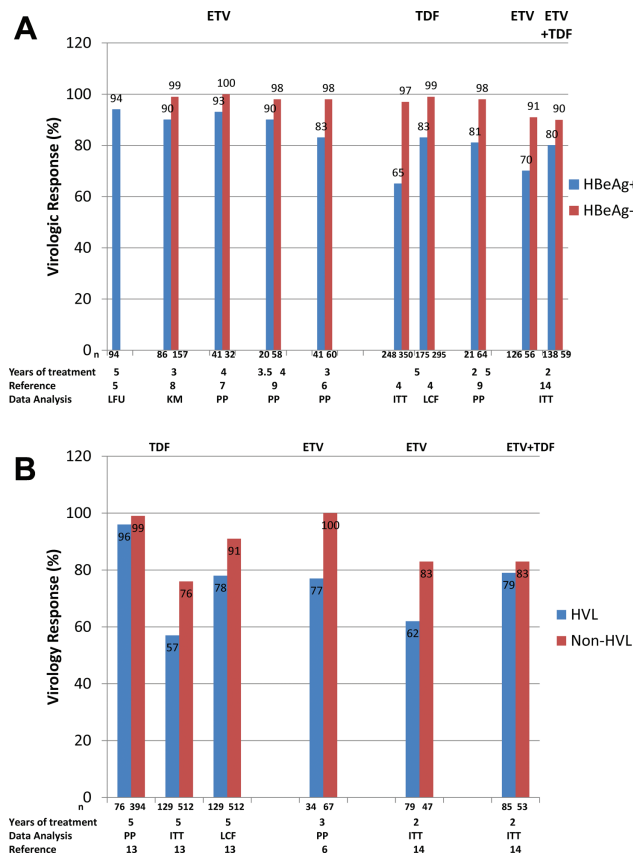


Fig. 1. Virologic response after 2-5 years of treatment with entecavir (ETV) or tenofovir disoproxil fumarate (TDF) monotherapy or combination of ETV plus TDF in nucleos(t)ide-naïve patients with chronic hepatitis B, (A) HBeAg+ and HBeAg- patients, and (B) patients with high versus not high viral load (HVL). Different definitions were used for virologic response and high viral load in different studies. LFU = subset of patients with long-term follow-up; KM = Kaplan-Meier probability of response; PP = per protocol analysis of patients with data at that timepoint; ITT = intention to treat analysis with missing data counted as failure; LCF = last result carried forward.

resistance such as TDF is sufficient in maintaining viral suppression during long-term treatment even in patients with HVL. However, the results should be interpreted with caution. Persistent viremia in this study was defined as never having HBV DNA <400 copies/mL and this endpoint was only reported on patients who remained on treatment at Week 240. Thus, patients with HBV DNA <400 copies/mL at a single timepoint and higher levels of HBV DNA subsequently would not be considered to have persistent viremia and those who were no longer on treatment at Week 240 were not counted. Of the 129 patients with baseline HVL, 46 discontinued the study before Week 240 of whom 28 had HBV DNA <400 copies/mL at the last visit. In the remaining 83 patients, 73 had HBV DNA <400 copies/mL, three had HBV DNA \geq 400 copies/mL, and HBV DNA of the other seven were unknown at Week 240. Thus, based on intention

to treat analysis, only 56.6% (73/129) patients had HBV DNA <400 copies/mL at Week 240. If the last result was carried forward, 78.3% (101/129) patients had HBV DNA <400 copies/mL. By contrast, HBV DNA <400 copies/mL at Week 240 was achieved in 76.0% (389/512) non-HVL patients by intention to treat analysis and in 91.0% (466/512) if the last result was carried forward. Furthermore, 35 HVL patients were eligible to add FTC between Week 72 and 240 and 28 eligible plus one noneligible patient had FTC added. Adding FTC did not appear to affect HBV DNA outcomes, with 66% (19/29) on FTC/TDF and 86% (6/7) on TDF having HBV DNA <400 copies/mL at Week 240 or last visit. The difference was not statistically significant but this may be related to the small number of patients. HBV DNA levels of the 11 patients with HBV DNA \geq 400 copies/mL were not provided.

That patients with HVL take longer to achieve virologic response had also been observed by other investigators. Yuen et al.⁶ studied 222 NUC-naïve patients and found that 100% and 76.5% of patients with baseline HBV DNA < and \geq 8 log₁₀ copies/mL, respectively, had undetectable HBV DNA at Year 3 of ETV therapy. The only patient in whom ETV resistance was detected had baseline HBV DNA 8.1 log₁₀ copies/mL. In a randomized trial comparing ETV monotherapy versus combination of ETV plus TDF in NUC naïve patients, Lok et al.¹⁴ showed that 76.4% and 83.2% patients, respectively, achieved the primary endpoint of HBV DNA <50 IU/mL (\sim 300 copies/mL) at Week 96 ($P = 0.088$). However, a significant difference was observed at Week 96 in HBeAg-positive patients with HVL (defined as HBV DNA 8 log₁₀ IU/mL), 62.0% versus 78.8% ($P = 0.018$) and in the entire cohort at Week 48, 70.3% versus 80.2% ($P = 0.026$).

A key question is whether more rapid suppression of HBV replication is clinically relevant. Rapid viral suppression is important in preventing antiviral drug resistance when NUCs with a low barrier to resistance such as lamivudine or telbivudine are used.^{15,16} The impact seems to be small with ETV or TDF. Rapid viral suppression may be important in patients with acute liver failure, severe exacerbation of chronic hepatitis B, or decompensated cirrhosis but there is no evidence to support this notion. Rapid viral suppression may also be important in patients with high levels of HBV DNA who are about to start immunosuppressive therapy; however, data to substantiate this are not available.

In summary, existing data support that initial treatment with combination NUCs is not necessary for the

vast majority of patients with chronic hepatitis B when ETV or TDF is used, and while combination therapy may accelerate viral suppression in patients with high baseline viral load, in most instances the marginal clinical benefit does not justify the added cost.

ANNA SUK-FONG LOK, M.D.
University of Michigan
Ann Arbor, MI

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